REMARKS

The Office Action mailed on July 23, 2007 has been reviewed and the comments of the Examiner carefully considered. Claims 2, 6, and 22 are pending in this application and currently stand rejected as more fully described below. Claim 2 has been amended. This amendment has been made solely to expedite prosecution without any admission as to the propriety of the rejections. Support for the amendment may be found, for example, at page 40, lines 20-22 and at page 41, lines 6-14 of the specification. No new matter has been added by way of this amendment.

Rejections under 35 U.S.C. § 103(a)

Claims 2, 6, and 22 stand rejected by the Examiner under 35 U.S.C. § 103(a) as being unpatentable over Berd et al. (WO 96/40173) in view of Sensi et al. (J. Clin. Invest. 1997; 99: 710-717). The Office Action contends that it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to modify the method taught by Berd et al. so as to administer a single dose of cyclophosphamide in view of the teachings of Sensi et al. because Sensi et al. teach that patients showed a therapeutic benefit from receiving a single dosage of cyclophosphamide 3 days prior to a six-week administration of DNP-vaccine.

Applicant respectfully disagrees. However, in the interest of facilitating the prosecution of this application, independent claim 2 has been amended to require: "administering a single dose of cyclophosphamide to a human, followed by at least six weekly administrations of a composition comprising a therapeutically effective amount of a hapten modified, irradiated autologous colon carcinoma cell and an adjuvant wherein said adjuvant is Bacille Calmette-Guerin, and further followed by at least one booster vaccine."

Berd et al. does not teach a method of treating colon carcinoma consisting of administering a single dose of cyclophosphamide, followed by at least six weekly administrations of a composition comprising a therapeutically effective amount of hapten modified, irradiated autologous colon carcinoma cell and an adjuvant, and further followed by at least one booster vaccine. Sensi et al. does not teach that an administration of a single dose of cyclophosphamide three days prior to a six-week administration of DNP-vaccine produces a therapeutic effect in comparison to an administration schedule where DNP-vaccine was

administered every 28 days with cyclophosphamide administered before the first two vaccine injections. Of the five patients (FC, CB, JB, RS, LC) given the six-week administration schedule, only one patient (JB) underwent any tumor regression – although this patient ultimately succumbed to metastatic melanoma in other visceral sites. The single patient (ED) on the 28-day administration schedule had a mixed response (regression of some subcutaneous tumors simultaneously with growth of others).

Sensi et al. is also directed specifically to melanoma, whereas the present claims are directed to colon carcinoma. There is no teaching or suggestion in Sensei that would motivate one of skill in the art to combine the teachings in Sensei for melanoma with the teachings of Berd et al for colon carcinoma. Due to the small pool of test patients and the mixed results of Sensi et al. as well as the histological and immunobiological differences between melanomas and carcinomas, one of ordinary skill in the art would not have had a reasonable expectation of success that a haptenized, autologous vaccine that works in melanoma would have any chance of being effective against colon cancer.

Furthermore, one of skill in the art will understand that different tumor types may react differently to the same or similar vaccine. For example, melanoma is considered to be an immunogenic tumor that may be susceptible to destruction by an immune response stimulated by a vaccine. The evidence for the particular immunogenicity of melanoma includes the following: (1) metastatic melanomas sometimes regress spontaneously[1] while this phenomena is has not been documented with metastatic colon carcinoma[2]; (2) primary melanoma of the skin commonly shows clinical and histological signs of regression and these are associated with infiltration of T-lymphocytes[3] while regression of primary colon carcinomas has not been observed; and (3) metastatic melanomas sometimes respond to treatment with immune

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[1] Bodurtha AJ, Berkelhammer J, Kim YH, Laucius JF, Mastrangelo MJ. A clinical, histologic, and immunologic study of a case of metastatic malignant melanoma undergoing spontaneous remission. *Cancer*, 1976; 37:735-42.

[2] Everson TC, Cole WH. Spontaneous regression of cancer; a study and abstract of reports in the world medical literature and of personal communications concerning spontaneous regression of malignant disease. Philadelphia: Saunders; 1966.

[3] Elder DE, Ainsworth AM, Clark WH, Jr. The surgical pathology of cutaneous malignant melanoma. In: Clark WH, Jr., Goldman LI, Mastrangelo MJ, editors. Human malignant melanoma. New York: Grune and Stratton; 1979. p. 55-108.

stimulating drugs such as interleukin-2[4] and α-interferon[5] while metastatic colon cancers do not. For at least these reasons, there are comparatively few studies of DNP-modified autologous vaccines in patients with colon cancer. Finally, none of the references teach or suggest at least one booster vaccine.

For at least the reasons articulated above, the combination of these references does not render claims 2, 6 and 22 obvious. The Applicant respectfully requests that this rejection be reconsidered and withdrawn.

Claims 2, 6, and 22 also stand rejected by the Examiner under 35 U.S.C. § 103(a) as being unpatentable over Hoover et al. (*Cancer*, 1985; 55: 1236-1243) and Berd (U.S. Patent No. 5,290,551). The Office Action contends that it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to modify the method taught by Hoover et al. so as to haptenize the irradiated autologous colon carcinoma cells in view of the teachings of Berd et al.

Applicant respectfully disagrees. For at least the reasons cited above, the Applicant submits that none of the references relied upon, either alone or in combination, disclose, teach, or suggest a method of treating colon carcinoma consisting of administering a single dose of cyclophosphamide, followed by at least six weekly administrations of a composition comprising a therapeutically effective amount of hapten modified, irradiated autologous colon carcinoma cell and an adjuvant, and further followed by at least one booster vaccine. Berd is directed to melanoma rather than carcinoma. Further, the method of Hoover et al. involved an autologous, non-hapten-modified vaccine that was not effective in prolonging the survival of patients to whom it was administered in a post-operative adjuvant setting.[6] A major technical problem with Hoover et al. was that a majority of the colon cancer vaccines were contaminated with bacteria.[7]

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[4] Rosenberg SA. Progress in human tumour immunology and immunotherapy. *Nature* 2001. May 17; 411(6835):380-4.

[5] Creagan ET, Ahmann DL, FRYTAK S, LONG HJ, Itri LM. Recombinant leukocyte α-interferon in the treatment of disseminated melanoma. *Cancer* 1986; 58:2576-8.

[6] Harris JE, Ryan L, Hoover HC, et al. Adjuvant active specific immunotherapy for stage II and III colon cancer with an autologous tumor cell vaccine: Eastern Cooperative Oncology Group Study E5283. *J Clin Oncol* 2000; 18:148-57.

[7] Vermorken JB, Claessen AME, van Tinteren H, Gall HE, Ezinga R, Meijer S, et al. Active specific immunotherapy for stage II and stage III human colon cancer: a randomised trial. *Lancet* 1999; 353:345-50.

Such contamination may interfere with the efficacy of the vaccine and make it unsafe to administer to patients. Moreover, bacterial contamination would have undoubtedly obscured the results of immunological testing of patients who received the vaccine because the bacteria, or endotoxin produced by the bacteria, would be expected to produce a false-positive response in the delayed-type hypersensitivity assay used by Hoover et al.[8]

Therefore, the combination of these references cannot render claim 2 obvious because none of the references teach or suggest all of the elements of claim 2, as amended. A combination of references that fails to yield the claimed invention cannot make the claim obvious. In addition, for at least the reasons cited above, one of ordinary skill in the art would have understood that it would take experimentation with the DNP-modified vaccine to determine whether the method could be applicable to colon cancer. Administering at least six weekly administrations of a composition comprising a therapeutically effective amount of hapten modified, irradiated autologous colon carcinoma cells and an adjuvant followed by at least one subsequent booster vaccine, increases the efficiency of the vaccine process, results in an increase in the number and capacity of T-lymphocytes to infiltrate into the tumor mass, maintains the immunologic reaction resulting in prolonged relapse times and/or total survival, and increases the effectiveness of the resulting tumor-specific immune response resulting in a more effective immunotherapy.

Accordingly, the Applicant respectfully submits that at least for the foregoing reasons, claim 2 is allowable as written over the cited references, and that claims 6 and 22 are allowable over the cited references as depending from an allowable claim.

[8] Harris JE, Ryan L, Hoover HC, et al.

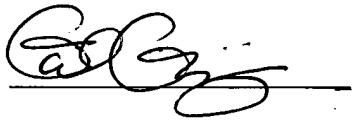
Conclusion

Applicant believes that the claims are in condition for allowance. An early Notice of Allowance is therefore earnestly solicited. Applicant invites the Examiner to contact the undersigned at (215) 963-5265 to clarify any unresolved issues raised by this response.

Respectfully submitted,

DAVID BERD

Date: 23 January 2008

By: 

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